

# PATENT SPECIFICATION

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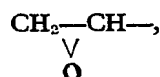
## COMPLETE SPECIFICATION

### Process for the Manufacture of Hydrophilic High Molecular Weight Substances from Dextran Substances

We, AKTIEBOLAGET PHARMACIA, a Swedish Company, of 2, Sofielundsgaten, Uppsala, Sweden, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to a process for the manufacture of hydrophilic high molecular weight substances by polymerization of dextran substances, whereby products are obtained which according to degree of polymerization and hydrophilicity possess valuable properties for different purposes of utilization.

The process according to the invention comprises reacting a hydroxyl group-containing dextran substance with a bifunctional aliphatic compound containing from 1 to 10 carbon atoms the chain of carbon atoms of which may be interrupted by ether groups and containing halogen atoms and/or epoxy groups at the end of the chain, for example



which react with the hydroxyl groups of the dextran with formation of linkages of ether type, so that a polymerization product containing at least two of the molecules of the dextran substance bound together with ether bridges is obtained.

The term "dextran substances" used in the present specification and in the appended claims is intended to comprise dextran as well as hydrophilic hydroxyl group-containing derivatives of dextran. For example, as dextran substances in the reaction may be used native dextran or partially depolymerized dextran or neutral hydroxyl group-containing hydrophilic derivatives of dextran or partially depolymerized dextran, such as ethyl-, hydroxyethyl or 2 - hydroxy - propylether of dextran

or dextran glycerine glycoside, or hydrodextran (i.e. dextran, the reducing end groups of which have been reduced to alcohol groups), or hydroxyl group-containing hydrophilic derivatives of dextran or partially depolymerized dextran containing acid or basic groups, for example, carboxyl groups, sulphonic acid groups, or amino groups or substituted amino groups, such as carboxymethyldextran or dextran, the end groups of which are oxidized to carboxyl groups. Often also fractions of the above-mentioned dextran substances may advantageously be used.

As examples of suitable bifunctional substances for carrying out the process may in the first place be mentioned bifunctional glycerine derivatives, such as epichlorohydrin, dichlorohydrin, epibromohydrin and dibromohydrin, further 1,2 - 3,4 - diepoxybutane, diepoxypropylether, diepoxypropylethers of ethylene-glycol, propyleneglycol, polyethylene glycols and similar compounds. Generally, aliphatic diepoxy compounds containing carbon, hydrogen, oxygen and without dissociable groups are suitable for the purpose.

The reaction is suitably carried out in the presence of a solvent in which at least one of the reacting components is soluble, preferably water, but also organic solvents, such as dimethylformamide may be used. Further, it has been found suitable to add an alkaline reacting substance having a catalyzing effect and as examples hereof may be mentioned alkali metal hydroxides and alkaline earth metal hydroxides. Other examples of catalysts are tertiary and quaternary amines.

In the reaction two or more of the molecules of the dextran substances are bonded together to larger molecules with formation of ether bridges of the type  $R_1-O-X-O-R_2$ , wherein  $R_1$  and  $R_2$  represent radicals or residues of molecules of the dextran substance and X is the bridge obtained from the bifunctional organic substance. If a bifunctional

- glycerine derivative, for example epichlorohydrin, is used the bridge will be of the type  $R_1-O-CH_2-CH(OH)-CH_2-O-R_2$ . If three dextran substance radicals are bonded together by means of two bridges, the product will be of the general type  $R_3-O-X-O-R_4-O-X-O-R_5$ , wherein  $R_3$ ,  $R_4$  and  $R_5$  are the dextran substance radicals and X represents the bridges.
- By varying the reaction conditions, for example the molecular weight of the dextran substance used as the starting material, and the proportions of the reaction components, high molecular weight products with very different average molecular weights and different properties in other respects may be obtained. For example, it is possible to obtain high molecular weight polymerization products which are water-soluble or also products in the gel form. The gels obtained in this way consist of three dimensional networks of macroscopic dimensions of the molecules of the dextran substance bonded together by covalent linkages, said substances being insoluble in the solvent but capable of absorbing solvent with swelling. This capacity of swelling may be expressed by the factor of swelling. Measurements of this may be made for example by suspending a weighed quantity of dry gel grains in a solvent in a graduated cylinder and then allow the grains to settle until the upper level has been stabilized. The volume of the sediment is then read off and the volume in ml so obtained is divided by the originally weighed quantity of gel in grams. This quotient is defined as the factor of swelling.
- If the other factors in the reaction are kept constant the factor of swelling of the gel is proportional to the content of solvent, inversely proportional to the content of bifunctional organic substance, and inversely proportional to the molecular weight of the dextran substance.
- As example may be mentioned that dextran with an average molecular weight of about 2000 in 60% aqueous solution reacted with 10% epichlorohydrin, based on the quantity of the dextran, does not give a gel, while dextran with the average molecular weight of 40,000 in 50% solution reacted with 4% of epichlorohydrin gives a polymerization product of in the form of a gel.
- As indicated above, the reaction is preferably carried out in the presence of water and an alkaline catalyst which may suitably be dissolved in the water. However, generally the content of water in the reaction should be as low as possible to avoid undesirable side reactions. The reaction may be carried out either with the dextran substance in solution, which especially in case of using native dextran may be very viscous, or with the dextran substance in particle form swollen by water. When using an aqueous solution the concentration of the dextran substance should be at least 5% and preferably exceed 10%, but it may also be much higher. If halogen hydrins are used as bifunctional organic substances, the amount of alkali must be sufficient to neutralize the hydrogen halogen split off in the reaction.
- The reaction temperature may be varied within wide limits and hereby naturally the reaction time to a certain degree will be dependent on the reaction temperature which has been chosen. With regard to the speed of reaction it is advisable not to work at too low a temperature. However, on the other hand, to prevent undesirable side reactions, the temperature should not be too high, and in view hereof, it may in certain cases also be suitable to carry out a cooling. With due consideration to these circumstances it is preferred to carry out the reaction between room temperature of 60—90°C.
- According to the desired average molecular weight and the other properties of the product to be manufactured, is possible to choose the proportions of the reacting substances and the other reaction conditions in such a way that the desired product is obtained when the reaction proceeds to the end, or also the reaction may be interrupted at a stage when a product with the desired average molecular weight has been obtained.
- In certain cases it may be suitable to carry out the reaction in two or more steps, for example in such a way that the reaction is interrupted in such a stage when the bifunctional substance has reacted only partly, for example when one of its reactive groups has reacted and been bound to the growing polymer, while the other reactive groups has not yet reacted, whereupon the conversion is completed in a later step. It is also possible to proceed in such a way that the dextran substance is caused to react with amounts of the bifunctional substance which are added successively stepwise, whereby the average molecular weight of the product is increased in steps. This manner of working is especially suitable when it is desired to subject the product to a purifying treatment before the molecular weight, and as a consequence thereof of the viscosity, has become very high, which will render the treatment of the product difficult.
- The purification of the high molecular weight products produced according to the invention naturally has to be effected in different manners dependent of whether the products are soluble or not. In the case of soluble products the purification as well as fractionation of the polydisperse reaction product may be effected in the usual manner, for example by precipitation with suitable precipitating agents, such as alcohols or ketones, for example ethyl alcohol, isopropyl alcohol or acetone, or other substances in which the product is sparingly soluble. Other methods which may be applied for the treatment of soluble

reaction products are extraction with water containing non-solvents, or purification by the aid of ion exchangers or dialysis.

In the case of insoluble products, these should first be ground down to such a particle size that the purification is not rendered difficult due to the fact that the diffusion equilibrium is reached too slowly. The purification may then be effected in a Buchner funnel or a centrifuge or the like by washing with water or organic solvents. It is important that some water is present, since the gel in a completely unswollen state often contains impurities enclosed mechanically which, however, when the gel under the influence of the water swells, can pass out of the gel particles by diffusion.

If in the polymerization products having too high average molecular weights are obtained, said products may be subjected to a partial depolymerization, for example by a mild hydrolysis, for example by the aid of an acid, or alcoholysis, and thus reduced to the desired lower average molecular weight. Such a partial hydrolysis may suitably be carried out in 0.1 normal HCl at 80°C and be interrupted when the depolymerization to the desired average molecular weight has been obtained, similarly as in the known partial depolymerization of dextran. As an example may be mentioned a partial breakdown from an average molecular weight of 100,000 to an average molecular weight of 80,000. Naturally, products of a very high molecular weight, as well as also gels, may be partially hydrolyzed down to the desired molecular weight.

The high molecular weight products obtained according to the invention may, if soluble, be characterized for example by determination of their average molecular weight ( $M_w$ ), for example by light scattering measurements. Sometimes it may be suitable to determine the distribution of the molecular weight. It is also possible to determine the intrinsic viscosity ( $\eta$ ) defined by

$$\lim_{c \rightarrow 0} \frac{\eta_{sp}}{c}$$

where  $[\eta]_{sp}$  is the specific viscosity (=relative viscosity - 1) and  $c$  is the concentration of the high molecular weight product, for example expressed in g/100 ml solution, or determine the viscosity at a given concentration relative to water. If the products are gels, they may suitably be characterized by their factors of swelling.

As indicated above, the high molecular weight products manufactured according to the invention have proved to possess valuable properties for different purposes of utilization. For example, the soluble polymers may be used for therapeutic and pharmaceutical purposes, for example as plasmasubstitute, as agents to counteract so-called "sludge" in the blood ves-

sels, for different permeability investigations, such as kidney function tests, as water keeping agents and suspension stabilizing and viscosity regulating agents in pharmaceutical and chemotechnical preparations. In view of the fact that in the process of the invention it is possible to start from dextran substances with extremely varying molecular weights, from very low to extremely high molecular weights, it is possible to obtain final products with very varying properties according to the desired field of application. Due to the fact that in the dextran substances the glycoside linkages are mostly 1:6 - linkages, said linkages are comparatively resistant to hydrolysis and are not decomposed by amylases.

The gel may be used as disintegrating agents for tablets, as water keeping laxatives and as fillers in pharmaceutical and chemotechnical preparations etc. They have proved to be extremely valuable for separation of substances of different molecular dimensions, by so-called molecular sieving. They may also be used as base substances for the manufacture of ion exchangers. Further, if they contain acid or basic groups, for example carboxyl groups, sulphonic acid groups or amino groups, they may directly be used as ion exchangers with valuable properties.

Especially useful products are obtained if the polymerization is carried on so far that the product obtained, maybe after fractionation and/or partial depolymerization, has an average molecular weight within the limits 2000—100,000,000, preferably within the limits 5000—10,000,000, for example between the limits 10,000—1,000,000.

Especially for the manufacture of products for medical or pharmaceutical purposes, for example colloidal infusion solutions, the polymerization may suitably be carried on so far that a product is obtained, having an average molecular weight, if desired after fractionation, within the limits 10,000—500,000, preferably within the limits 20,000—300,000, for example within the limits 30,000—200,000.

According to the desired purpose of utilization, the product may be subjected more or less to a fractionation and a sufficient purification, so that a product with suitable average molecular weight and sufficient degree of purity for the purpose in question is obtained. As an example may be mentioned a product having an average molecular weight of about 70,000.

When the products are to be used for injection and infusion purposes for medical application, for example in colloidal infusion solutions, such as plasmasubstitute, it is important that they have a suitable distribution of the molecule weights, which may be obtained for example by fractionation, if required, since very high molecular weight substances cause not desired side reactions and

since it is desirable to avoid too much low molecular weight substances left in the product, since too small molecules after infusion are rapidly filtered out from the blood.

- 5 Products having a suitable molecular weight which have been obtained from smaller dextran molecules by synthesis to larger molecules in accordance with the invention, possess in comparison with the common dextran with corresponding molecular weight certain advantages which are to be ascribed to another form and modified properties of the molecules. Thus, for example, such synthetic products cause less agglutination of the blood corpuscles and have a less pronounced influence on the erythrocyte sedimentation rate. In comparison with the common dextran it also has a modified influence on the blood coagulation mechanism and modified serological properties.
- 10 Such products of a sufficiently low molecular weight (for example 30,000) further possess the valuable property to counteract the formation of so-called "sludge" when they are infused into the blood vessels. In addition, these products are characterized by their low toxicity.

- By means of the present invention it is also possible to convert to valuable products the valueless low molecular fractions of dextran which are obtained as a waste in the usual manufacture of plasmasubstitute from dextran, by coupling together such very small dextran molecules to molecules of the desired size.

- The invention will now be more particularly described by reference to the following examples.

#### EXAMPLE 1

60 g of dextran having the average mole-

cular weight ( $M_w=2000$ ) were dissolved in 40 ml of 5N NaOH - solution. After addition of 6 g of epichlorohydrin, the solution was stirred for 48 hours at room temperature. After neutralization and repeated precipitations with ethanol, 38 g of a product having the average molecular weight 4900 was obtained.

#### EXAMPLE 2

To an aqueous solution of dextran having the intrinsic viscosity ( $\eta$ )=0.16 ( $M_w=25,000$ ) containing 36.8 g of dextran per 100 ml solution 5.5 g epichlorohydrin and 10 ml 33% solution of sodium hydroxide were added. At the beginning of the experiment the temperature was 60° C, but it rose rapidly to 80° C. After 1 hour the experiment was discontinued by cooling and neutralization. The product was purified by several reprecipitations from aqueous solutions with ethanol. It had an intrinsic viscosity of 0.35 and an average molecular weight of 170,000.

#### EXAMPLE 3

700 g of dextran of the same kind as in the previous example were dissolved in water to a concentration of 34.5 g per 100 ml. To this solution 80 g of epichlorohydrin and 80 ml 33% solution of sodium hydroxide were added. In 5 minutes the temperature rose from 60° C to 91° C and during the following 10 minutes the temperature sank to 85° C. After 1 hour the experiment was discontinued by cooling and neutralization. The product was purified by precipitation twice with ethanol. Its intrinsic viscosity ( $\eta$ ) was 0.26. The product was fractionated by successive additions of ethanol and hereby the following fractions were obtained.

Fraction	Weight g	%	( $\eta$ )	$M_w$
1	51.5	7.6	0.484	
2	28.4	4.2	0.404	
3	367.0	53.8	0.265	120,000
4	119.0	17.4	0.136	
5	116.0	17.0	0.110	

#### EXAMPLE 4

- 500 g of dextran ( $M_w=40,000$ ) were dissolved in 1170 ml N solution of sodium hydroxide and 100 g epichlorohydrin were added thereto. After 2 hours at 45° C a gel had been formed, which was hardened by heating to 45° C for 24 hours. After grinding, neutralization, washing and drying 560 g of a product with the factor of swelling 10 ml/g were obtained.

#### EXAMPLE 5

500 g of dextran ( $M_w=40,000$ ) were dissolved in 2000 ml N solution of sodium hydroxide and 100 g of epichlorohydrin were added thereto. After 4 hours at 45° C a gel had been formed which was hardened by heating to 45° C for 24 hours. After grinding, washing and drying, 360 g of a product with the swelling factor 24 ml/g were obtained.

## EXAMPLE 6

500 g of dextran ( $M_w=40,000$ ) were dissolved in 2000 ml of N solution of sodium hydroxide and 185 g of epichlorohydrin were added there to. After 4 hours at 45°C. a gel had been formed which was hardened by heating to 45°C for 24 hours. After grinding, neutralization, washing and drying, 574 g of a product having the factor of swelling 13 ml/g were obtained.

## EXAMPLE 7

500 g of dextran ( $M_w=1,800,000$ ) were dissolved in 2000 ml N solution of sodium hydroxide and 100 g of epichlorohydrin were added thereto. After 1 hour at 45°C a gel had been formed which was hardened by heating to 45°C for 24 hours. After grinding, neutralization, washing and drying, 540 g of a product with the factor of swelling 19 ml/g were obtained.

## EXAMPLE 8

100 g of dextran ( $M_w=1,800,000$ ) were dissolved in 2000 ml of 0.5 N solution of sodium hydroxide and 100 g of epichlorohydrin were added thereto. The mixture was heated for 8 hours to 55°C. Hereby a gel was formed. After grinding, neutralization, washing and drying, 60 g of a product with the factor of swelling 85 ml/g were obtained.

## EXAMPLE 9

120 g of dextran ( $M_w=5000$ ) were dissolved in 80 ml of 5 N solution of sodium hydroxide and 24 g of epichlorohydrin were added thereto. After 24 hours at room temperature the mass had solidified to a gel which was hardened by heating to 40°C for 24 hours. After grinding, neutralization, washing and drying, 74 g of a product with the swelling factor 16 ml/g were obtained.

## EXAMPLE 10

1 kg of dextran ( $M_w=40,000$ ) were dissolved in 1 litre of 4 N solution of sodium hydroxide and 550 g of epichlorohydrin were added thereto. The temperature rapidly rose to 70°C and this temperature was maintained for 24 hours. After grinding, neutralization, washing and drying, 1.1 kg of a product with the factor of swelling 3.5 ml/g were obtained.

## EXAMPLE 11

To a solution of 20 g of dextran ( $M_w=40,000$ ) in 80 ml water 0.5 ml of 5 N solution of sodium hydroxide and 17 g of ethylene glycol - bis - epoxypropylether were added. The mixture was heated for 24 hours to 70°C. After 2 hours a gel had been formed. After grinding, washing and drying, 28 g of a product having the factor of swelling 7.5 ml/g were obtained.

## EXAMPLE 12

To 50 g of dextran ( $M_w=40,000$ ) in powder form which had been swollen by addition of 20 ml of 5 N solution of sodium hydroxide, 10 g of epichlorohydrin were added. The

powder mass was kneaded at 50°C for 16 hours, after which time it had become insoluble in water. After decantation, washing and drying, 52 g of a product with the factor of swelling 18 ml/g were obtained.

## EXAMPLE 13

To a solution of 100 g of dextran ( $M_w=1,800,000$ ) in 500 ml of 2 N solution of potassium hydroxide 30 g of glycerine - 1,3 - dichlorohydrin were added at room temperature. After 15 minutes a gel had been formed.

## EXAMPLE 14

60 g of dextran ( $M_w=40,000$ ) were dissolved in 140 ml water, whereupon 50 g of solid calcium hydroxide and 25 g of epichlorohydrin were added thereto. After 2 hours at room temperature a gel had been formed. It was hardened by heating to 60°C for 72 hours. After grinding, washing and drying, 68 g of a product with the factor of swelling 8.2 ml/g were obtained.

## EXAMPLE 15

25 g of sodiumcarboxymethyldextran ( $M_w=40,000$ ) were dissolved in 25 ml of 2 N solution of sodium hydroxide, and 5 g of epichlorohydrin were added thereto. After 1 hour at room temperature a gel had been formed. It was hardened at 60°C for 48 hours. The factor of swelling of the product so obtained was 7 ml/g.

## EXAMPLE 16

40 g of 2 - hydroxypropyldextran ( $M_w=40,000$ ) were dissolved in 40 ml of 2 N solution of NaOH, and 8 g of epichlorohydrin were added thereto. The solution was left to stand at room temperature over night and hereby a gel was formed. It was hardened at 60°C for 48 hours. The factor of swelling of the product so obtained was 15 ml/g.

## EXAMPLE 17

50 g of hydrodextran ( $M_w=40,000$ ) were dissolved in 50 ml of 2 N solution of sodium hydroxide, and 8.9 g of epichlorohydrin were added thereto. After 2 hours at room temperature a gel had been formed. It was hardened at 45°C for 72 hours. After grinding, washing and drying, 56 g of a product with the factor of swelling 7 ml/g were obtained.

## EXAMPLE 18

50 g of dextranglycerineglycosid ( $M_w=80,000$ ) were dissolved in 50 ml of 2 N solution of sodium hydroxide, and 10 g of epichlorohydrin were added thereto. After 2 hours a gel had been formed.

## EXAMPLE 19

50 ml of a 6% solution of the main fraction in Example 3 (No. 3/ $\eta=0.265$ ) were fractionated by successive additions of ethanol as stated in the table below. Each fraction was dried and weighed, whereupon its intrinsic viscosity was determined.

Fraction No.	Abs. alcohol ml	Fraction weight mg	( $\eta$ )
1	48.0	772	0.395
2	0.8	378	0.330
3	1.5	535	0.296
4	2.5	584	0.258
5	3.5	521	0.224
6	4.5	338	0.190
7	evaporated	734	0.144

Fraction No. 7 was obtained by evaporation of the mother liquor from fraction No. 6.

#### EXAMPLE 20

From the main fraction (No. 3,  $\eta = 0.265$ ) obtained in Example 3 a solution containing 6% of the product of said fraction and 0.9% sodium chloride was prepared. A quantity thereof corresponding to 1 g per kg body weight was administered intravenously in a rabbit. The urine was collected and the content of dextran product therein was determined polarimetrically. During the first 24 hours 35% of the infused quantity of dextran product was separated off in the urine and during the next 24 hours 2%.

#### WHAT WE CLAIM IS:—

1. A process for the manufacture of hydrophilic high molecular weight substances from dextran, characterized in that a hydroxyl group-containing dextran substance is reacted with a bifunctional aliphatic compound containing from 1 to 10 carbon atoms the chain of carbon atoms of which may be interrupted by ether groups and containing halogen and/or epoxy groups at the ends of the chain, which react with the hydroxyl groups of the dextran with formation of linkages of ether type, so that a polymerization product containing at least 2 of the molecules of the dextran substance bound together by ether bridges is obtained.

2. A process according to claim 1, wherein the dextran substance is native dextran or partially depolymerized dextran, or fractions thereof.

3. A process according to claim 1, wherein the dextran substance is a neutral hydrophilic derivative of dextran or partially depolymerized dextran, or fractions thereof.

4. A process according to any of the preceding claims, wherein the bifunctional organic substance is a bifunctional glycerine derivative, for example epichlorohydrin, dichlorohydrin,

epibromohydrin or dibromohydrin.

5. A process according to any of the preceding claims, wherein the reaction is carried out in the presence of a solvent, for example water.

6. A process according to any of the preceding claims, wherein the reaction is carried out in the presence of alkali metal hydroxide, alkaline earth metal hydroxide, or a tertiary or quaternary amine.

7. A process according to any of the preceding claims, wherein the reaction is carried out in an aqueous solution in which the concentration of the dextran substance is at least 5% and preferably exceeds 10%.

8. A process according to any of the preceding claims, wherein the polymerisation is carried on so far that a gel is formed.

9. A process according to claim 8, especially for the production of ion exchangers, wherein the dextran substance is a hydrophilic dextran derivative containing acid or basic groups.

10. A process according to any of the preceding claims 1—7 in the case when the high molecular weight product obtained is water-soluble, wherein the product is purified by precipitation and/or by treatment with ion exchangers.

11. A process according to any of the preceding claims 1—9 in the case when the high molecular weight product obtained consists of a gel, wherein the gel is divided into particles of suitable size and is then purified by washing with water.

12. A process according to any of the preceding claims 1—7, and 10 wherein the polymeric fraction product obtained is subjected to a fractionation by the aid of a precipitating agent in which the reaction product is sparingly soluble, so that fractions are obtained which are less polydisperse than the

starting product.

- 5 13. A process according to any of the preceding claims, wherein the polymerisation is carried on so far that the product obtained maybe after fractionation, has an average molecular weight within the limits 5000—10,000,000.

- 10 14. A process according to any of the preceding claims, wherein the product obtained is subjected to a partial depolymerisation for correcting the average molecular weight, such as a mild hydrolysis, for example by means of an acid.

- 15 15. A process according to any of the preceding claims, especially for the production of products for medicinal purposes, for example, for colloidal infusion solutions, wherein the reaction is carried on so far that the product obtained, maybe after fractionation, has an average molecular weight within the limits 20,000—300,000.

- 20 16. A process according to any of the preceding claims, wherein the reaction is carried out in two or more steps.

- 25 17. A copolymerisation product comprising a three dimensional macroscopic network of dextran substances, bonded together by

ether bridges of the general type  $-R-O-X-O-R-$ , wherein R represents the dextran substances and X is a hydrocarbon radical containing 1—10 carbon atoms, the chain of carbon atoms of which may be interrupted by ether groups, the said copolymerisation product being water-soluble. 30

18. A copolymerisation product in gel form, comprising a three dimensional macroscopic network of dextran substances, bonded together by ether bridges of the general type  $-R-O-X-O-R-$ , wherein R represents the dextran substances and X is a hydrocarbon radical containing 1—10 carbon atoms, the chain of carbon atoms of which may be interrupted by ether groups, the said copolymerisation product being water-insoluble, but being capable of absorbing water with swelling. 35 40 45

19. A process for the manufacture of hydrophilic high molecular weight substances from dextran substantially as described hereinbefore with special reference to any one of the Examples 1—18. 50

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